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Diabetes mellitus increases risk for colorectal adenomas in younger patients

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ing for date of exam and gender. ADR was 14.4% in those ages 40-49 years without DM, 30.4% in those ages 40-49 years with DM, and 32.0% in those ages 50-59 years without DM. Compared to those ages 40-49 years without DM, ADR was higher in those ages 40-49 years with DM (OR = 3.1; 95%CI: 1.5-6.4; $P = 0.002$) and those ages 50-59 years without DM (OR = 2.9; 95%CI: 1.5-5.6; $P = 0.002$). There was no difference between the ADR in those ages 40-49 years with DM and those ages 50-59 years without DM ($P = 0.83$).

CONCLUSION: DM was associated with higher risk of colorectal adenomas in patients ages 40-49 years. These subjects harbored as many adenomas as those at the standard screening age of 50-59 years without DM.

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Key words: Adenoma; Colorectal cancer; Diabetes mellitus; Colonoscopy; Risk factor

Abstract

AIM: To determine if diabetes mellitus (DM) is associated with increased risk of colorectal adenomas in younger subjects.

METHODS: This was a retrospective cohort study of 375 patients undergoing index colonoscopy at a single tertiary care center in the United States. Three cohorts of patients matched for exam date and gender were compared: (1) ages 40-49 years with DM; (2) ages 40-49 years without DM; and (3) ages 50-59 years without DM. Data collected included demographics, co-morbidities, colonoscopy and pathology results. Adenoma detection rates (ADR) were calculated and compared. Conditional logistic regression analysis was performed to determine the association between each cohort and ADR.

RESULTS: One hundred and twenty-five patients ages 40-49 with DM met study eligibility criteria. Patients in the other two cohorts were randomly selected, match-

Core tip: Diabetes mellitus (DM) is associated with increased risk of colorectal neoplasia. It is unknown if patients with DM should be screened more aggressively. Three cohorts were compared: patients aged 40-49 years with DM, 40-49 years without DM, and 50-59 years without DM. DM was associated with increased risk for developing colorectal adenomas in patients 40-49 years old. This is the first study to specifically examine these differences among patients with or without DM younger than the recommended colorectal cancer screening age of 50 years.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer affecting both men and women and second most common cause of cancer death in the United States. In 2011, there were an estimated 141000 new diagnoses of CRC and 49000 deaths associated with CRC^[1]. There has been a decline in the incidence of CRC over the past two decades, which has been attributed to screening by colonoscopy, and removal of pre-malignant colon polyps. The United States Preventive Services Task Force, Multi-Society Task Force, and American College of Gastroenterology guidelines recommend initiating CRC screening at 50 years of age for those at average risk, and earlier for those at increased risk, such as those with family history^[2-4]. The American College of Gastroenterology guidelines also recommend earlier screening in African-Americans and awareness of increased risk of CRC in patients with obesity and history of smoking^[4].

Diabetes mellitus type 2 (DM) has been found to be associated with a 20%-60% increased risk of CRC^[5,6]. It is postulated that insulin resistance and the resulting hyperinsulinemia may promote carcinogenesis directly by stimulating colonic cell growth^[7,8]. In addition, insulin is thought to act indirectly by up-regulating growth hormone receptors in the liver to increase levels of insulin-like growth factor (IGF)-1 and inhibiting IGF binding proteins which also results in elevated levels of free IGF-1^[7,8]. IGF-1 is theorized to then enhance cell proliferation and inhibit apoptosis, thus promoting tumor growth. Insulin and IGF-1 may also act through Ras activation which leads to increased sensitivity to growth factors in colonic cells and possible accelerated progression from adenoma to carcinoma^[7,8]. Observational studies have shown an increased CRC risk with hyperinsulinemia as well as with elevated IGF-1 levels^[9]. In addition, there have been data showing a similar association with adenomatous polyps, the precursor to CRC^[10-13].

There currently are no modifications in CRC screening guidelines for people with DM. In particular, it is unknown if patients with DM should be screened earlier than patients at average risk for CRC. The aim of this study was to determine if DM is associated with increased risk of developing colorectal adenomas in subjects ages 40-49 years compared to an age matched group without DM and to average risk non-diabetics at the standard screening age of 50 years or older. Our hypothesis was that patients with DM would have increased rates of adenomas compared to those without DM.

MATERIALS AND METHODS

The study was approved by the Washington University Institutional Review Board and Siteman Cancer Center Protocol Review and Monitoring Committee. We performed a retrospective cohort study of patients undergoing colonoscopy at a single center over a six-year period, comparing three cohorts matched for date of exam and gender: (1) ages 40-49 years without DM; (2) ages 40-49

years with DM; and (3) ages 50-59 years without DM.

Subjects were identified from an endoscopy database among patients undergoing index colonoscopies at Washington University in St. Louis, Missouri between June 1, 2005 and June 30, 2011. Medical records were reviewed to determine DM status. All patients ages 40-49 years with DM undergoing index colonoscopies within the study period were first identified. Patients in the other two cohorts were then randomly selected in a 1:1 ratio, matching for date of exam and gender. Inclusion criteria also included index (first) colonoscopy, colonoscopy completed to the cecum, and excellent or good bowel preparation. Exclusion criteria included incomplete colonoscopy, poor or fair bowel preparation, history of prior colonoscopy, inflammatory bowel disease, polyposis syndrome, prior colectomy, personal history of CRC, or family history of CRC in a first-degree relative.

Medical records were reviewed to obtain data on demographics including age, gender, ethnicity, and height and weight to determine body mass index (BMI). Presence or absence of DM was determined by medical history obtained by nurses at the time of colonoscopy and corroborated by review of medical records and medication lists. DM status was also reviewed in terms of type of diabetic medication used and hemoglobin A1C level (HgbA1C) as a marker of glycemic control. Co-morbidities including presence of hypertension, hyperlipidemia, tobacco use, and alcohol use were also recorded. Family history of CRC was determined by medical history obtained by nurses and interview by colonoscopist at the time of colonoscopy and corroborated by review of medical records. Colonoscopy and pathology reports were reviewed to obtain data on indication, bowel preparation quality, completeness of procedure to cecum, and polyp characteristics (number, location, size, and pathology). Histopathologic diagnoses were recorded; high risk state was defined as adenoma size ≥ 1 cm, number of adenomas ≥ 3 , villous features, or high grade dysplasia. If multiple polyps were placed in the same specimen container, then pathology reports were closely reviewed to ascertain correct histopathologic diagnosis of each polyp. Polyp and adenoma detection rates (ADR), defined as the proportion of screened subjects in whom at least one polyp or adenoma was identified respectively, were calculated for each cohort.

Statistical analysis

Statistical analyses include comparisons of patient demographics and clinical characteristics among the three cohorts and use regression models to determine association of group status with ADR, adjusting for patient demographics and clinical characteristics. ANOVA was used to compare continuous variables (age, body mass index) among the three cohorts, and χ^2 test or Fisher exact test was used to compare categorical variables (gender, ethnicity, hypertension, hyperlipidemia, indication) among the three groups. For regression analyses, conditional logistic regression model was used since the patients in different cohorts were matched by date of exam and gender. Con-

Table 1 Baseline characteristics

	40-49 yr without DM (<i>n</i> = 125)	40-49 yr with DM (<i>n</i> = 125)	50-59 yr without DM (<i>n</i> = 125)	<i>P</i> -value
Age (yr, mean \pm SD)	45.7 \pm 3.1	46.1 \pm 2.7	53.7 \pm 2.7	< 0.001
Gender (% Female)	63.2	63.2	63.2	1.0
Ethnicity (% African-American)	35.2	46.0	39.2	0.13
Body mass index (kg/m ² , mean \pm SD)	29.6 \pm 7.4	36.0 \pm 9.6	28.6 \pm 7.0	< 0.001
Hypertension (%)	40.8	76.6	46.8	< 0.001
Hyperlipidemia (%)	16.9	50.0	25.0	< 0.001
Indication (%)				
Screening	15.3	14.8	83.2	< 0.001
Gastrointestinal bleeding	41.9	45.9	7.2	< 0.001
Change in bowel habits	29.8	30.3	5.6	< 0.001
Abdominal pain	6.5	3.3	1.6	0.13
Other	2.4	3.3	1.6	0.69

DM: Diabetes mellitus.

ditional logistic regression analysis was performed to determine the association between each cohort and ADR. Variables included in the conditional logistic regression model for adjustment were ethnicity, BMI, tobacco, and alcohol. Sensitivity analyses after further allowances for hypertension and hyperlipidemia were also performed. Data analyses were performed by using SAS software version 9.2 (Cary, North Carolina, United States).

RESULTS

A total of 3749 patients between the ages of 40-49 years underwent index colonoscopy between June 2005 and June 2011. After manual review of medical records, we found that 193 patients ages 40-49 years had DM at the time of their colonoscopy, but 68 of these patients were excluded due to poor or fair bowel preparation. Therefore, 125 patients ages 40-49 years with DM met study eligibility criteria and were included in the study. We then randomly selected 125 patients ages 40-49 years without DM and 125 patients ages 50-59 years without DM, matching for date of exam and gender.

Baseline characteristics

Baseline characteristics of the three cohorts are found in Table 1. Mean age was 46 years in the two younger cohorts and 54 years in the older cohort. Gender was matched for in all three cohorts with 63.2% female. There was no difference in ethnicity among the three cohorts with 35.2% African-Americans in the younger cohort without DM, 46.0% with DM, and 39.2% in the older cohort. There were significantly greater rates of comorbid obesity (higher mean BMI), hypertension, and hyperlipidemia in the cohort with DM as expected. Among patients with DM, 77.7% were on oral hyperglycemic medications, 52.3% were on insulin, and mean HgbA1C was 7.4%.

Indication for colonoscopy was screening in 83% of the patients ages 50-59 years without DM and 15% in the younger cohorts. Nearly all of the screening colonoscopies in the younger cohorts were performed in patients

in their late forties close to the recommended age of 50 years to start CRC screening. All other colonoscopies were performed for diagnostic purposes including gastrointestinal bleeding, change in bowel habits, or abdominal pain.

Polyp and adenoma detection rates

The polyp and adenoma detection rates are found in Table 2. The ADRs were 14.4% in those ages 40-49 years without DM (17.4% in men, 12.7% in women), 30.4% in those ages 40-49 years with DM (39.1% in men, 25.3% in women), and 32.0% in those ages 50-59 years without DM (41.3% in men, 26.6% in women). Compared to those ages 40-49 years without DM, there was a statistically significant higher association between cohort and presence of adenoma in those ages 40-49 years with DM (adjusted OR = 2.6, 95%CI: 1.4-4.9; adjusted OR=3.1, 95%CI: 1.5-6.4; *P* = 0.002) and those ages 50-59 years without DM (adjusted OR = 2.8, 95%CI: 1.5-5.2; adjusted OR = 2.9, 95%CI: 1.5-5.6; *P* = 0.002) in both univariate and multivariate analyses. A slightly stronger association was found in men (adjusted OR = 4.7 in patients ages 40-49 years with DM, adjusted OR = 4.0 in those ages 50-59 years without DM) than in women (adjusted OR = 2.5 in patients ages 40-49 years with DM, adjusted OR = 3.3 in those ages 50-59 years without DM). Despite differences in terms of prevalence of hypertension and hyperlipidemia between the two younger cohorts, sensitivity analyses after further allowances for the two co-morbidities showed a similar significant association (OR = 3.2, 95%CI: 1.5-7.1) for patients ages 40-49 years with DM and (OR = 3.0; 95%CI: 1.5-5.9) for those ages 50-59 without DM. There was no statistically significant difference between cohort and presence of adenoma in those ages 40-49 years with DM and those ages 50-59 years without DM (*P* = 0.78 on univariate analysis and *P* = 0.83 on multivariate analysis).

High risk state

The prevalence of high risk state, defined as adenoma size \geq 1 cm, presence of high grade dysplasia or villous

Table 2 Polyp and adenoma detection rates

	40-49 yr without DM (n = 125)	40-49 yr with DM (n = 125)	50-59 yr without DM (n = 125)
Polyp detection rate (%)	31.2	49.6	50.4
Adenoma detection rate (%)	14.4	30.4	32.0
Univariate OR (95%CI)	1.0 (reference)	2.6 (1.4-4.9)	2.8 (1.5-5.2)
Multivariate OR (95%CI) ¹	1.0 (reference)	3.1 (1.5-6.4)	2.9 (1.5-5.6)

¹Analyses were adjusted for ethnicity, body mass index, smoking, and alcohol use; DM: Diabetes mellitus.

Table 4 Polyp characteristics among patients with adenomas (n = 96)

	40-49 yr without DM (n = 18)	40-49 yr with DM (n = 38)	50-59 yr without DM (n = 40)	P-value
Number of adenomas (mean)	1.5	1.7	1.5	0.69
Location (% proximal)	38.9	55.3	52.5	0.50
Advanced adenoma (%)	50.0	31.6	40.0	0.40
Size ≥ 1 cm (%)	33.3	18.4	32.5	0.30
Villous features (%)	27.8	13.2	15.0	0.36
High grade dysplasia (%)	0	2.6	2.5	0.79

DM: Diabetes mellitus.

features, or number of adenomas ≥ 3 in the three cohorts are found in Table 3. Prevalence of high risk state were 7.2% in those ages 40-49 years without DM (10.9% in men, 5.1% in women), 9.6% in those ages 40-49 with DM (10.9% in men, 8.9% in women), and 12.8% in those ages 50-59 years without DM (15.2% in men, 11.4% in women). Compared to those ages 40-49 years without DM, we found trends towards higher prevalence of high risk state in those ages 40-49 years with DM and those ages 50-59 years without DM, but these were not statistically significant. There was no statistically significant difference between the prevalence of high risk state in those ages 40-49 years with DM and those ages 50-59 years without DM ($P = 0.4$).

Polyp characteristics

Among patients with adenomas, mean number of adenomas per patient, location of adenomas, and prevalence of advanced adenomas were not statistically significant among the three cohorts (Table 4). There were one, zero, and two synchronous CRC found in the cohorts ages 40-49 years without DM, ages 40-49 years with DM, and ages 50-59 years without DM, respectively.

DISCUSSION

In this retrospective cohort study, DM was associated with a significantly higher risk of developing colorectal adenomas in patients ages 40-49 years. These subjects harbored as many adenomas as those at the standard screening age of 50-59 years without DM, with both of

Table 3 Prevalence of high risk state

	40-49 yr without DM (n = 125)	40-49 yr with DM (n = 125)	50-59 yr without DM (n = 125)
Prevalence of high risk state ¹ (%)	7.2	9.6	12.8
Univariate OR (95%CI)	1.0 (reference)	1.4 (0.6-3.4)	1.9 (0.8-4.5)
		$P = 0.5$	$P = 0.1$

¹High risk state was defined as adenoma number ≥ 3 , size ≥ 1 cm, high grade dysplasia, or villous features; DM: Diabetes mellitus.

these cohorts having significantly more adenomas than those ages 40-49 years without DM. To our knowledge, this is the first study to specifically examine these differences among patients with or without DM younger than the recommended CRC screening age of 50 years.

In a large population-based retrospective cohort study, Limburg *et al*^[14] showed an association between DM and increased CRC risk with a standardized incidence ratio of 1.39. Hu *et al*^[15] also demonstrated a similar association in the Nurses' Health Study. After 18 years of follow-up, relative risk for CRC was 1.43 in those with documented DM at baseline. A recent meta-analysis by Yuhara *et al*^[6] found that DM was an independent risk factor for CRC and was associated with an increased risk for CRC in both men and women even after controlling for smoking, obesity, and physical exercise with relative risk of 1.37.

Prior studies have also shown higher prevalence of adenomas, the precursor to CRC, in patients with DM compared to those without DM. In a prospective study, Schoen *et al*^[10] found an association between increased levels of insulin and IGF-1 and presence of colorectal adenomas as well as advanced adenomas in 458 asymptomatic patients who underwent flexible sigmoidoscopy. Elwing *et al*^[11] previously compared 100 women with DM to 500 controls without DM undergoing index colonoscopy and found that women with DM had higher rates of adenomas (37% *vs* 24%, OR = 1.82) and advanced adenomas (14% *vs* 6%, OR = 2.38). With multivariate analysis, they found that DM was an independent predictor for the presence of both adenomas and advanced adenomas. Eddi *et al*^[12] performed a retrospective case-control study of patients with or without adenomas and found that DM, insulin exposure, and thiazolidinedione use was associated with developing adenomas. More recently, Kanadiya *et al*^[13] performed a retrospective cross-sectional analysis of 405 patients with DM and 3038 without DM undergoing first colonoscopy. DM was associated with increased risk of adenoma (OR = 1.35) and ADR was higher in diabetics (29.3% *vs* 23.9%). However, none of these studies compared ADR in patients with or without DM in patients under the age of 50 years.

There is consensus among guidelines that CRC screening should be initiated in average-risk individuals starting at 50 years of age^[2-4]. The rationale for this threshold is that the risk of CRC and advanced adenomas is low in younger individuals. The reported incidence of

CRC per 100000 population rises from 45.9 at age 40-49 years, to 133.3 at age 50-59 years and 268.2 at age 60-69 years^[16]. In two screening colonoscopy studies performed in asymptomatic patients ages 40-49, the prevalence of advanced adenomas was found to be 2% and 3.5% with no cases of CRC^[17,18]. The evidence from our study shows that the existence of DM in patients ages 40-49 years increases their risk of adenomas and advanced adenomas to that of patients ages 50-59 years without DM.

Greater DM severity as determined by the need for insulin therapy and HgbA1C levels, a measure of DM control, has also been found to be associated with increased risk for both CRC as well as adenomas. In a prospective population study, Khaw *et al*^[19] reported a three-fold risk for CRC in known diabetics. In addition, they found that there was a 1.34 increase in relative risk with every 1% increase in HgbA1C concentrations. Yang *et al*^[20] demonstrated a two-fold increased risk of CRC in patients with DM on insulin therapy for greater than one year compared to non-insulin using patients with DM. Chung *et al*^[21] found that diabetic patients with adenomas showed significantly higher rates of chronic insulin therapy compared to age and sex-matched controls, and that chronic insulin therapy was associated with three times the risk of having colorectal adenomas among a cohort of 325 patients with DM who underwent colonoscopy. Siddiqui *et al*^[22] found that poorly controlled diabetics with HgbA1C $\geq 7.5\%$ had greater number of adenomas, more advanced lesions, greater use of exogenous insulin, and younger age of presentation in a retrospective cohort study of 652 male veterans with DM and adenomas. In our cohort with DM, 52% were on chronic insulin therapy and mean HgbA1C was 7.4, implying that at least half of our patients with DM qualified as having severe disease and were at higher risk for adenomas despite their relatively young age.

Our study had several limitations. It was a retrospective cohort study with inherent limitations in this design study. To date, there have been no reported prospective studies evaluating the development of adenomatous polyps in patients with DM or specifically those younger than the age of 50 years. There was also a relatively low sample size in each of the cohorts, likely due to low rates of diabetes in patients 40-49 years old. Another limitation of our study is that it was not performed in an average risk screening population. However, patients under the age of 50 years are currently not recommended to undergo screening colonoscopy unless they are at increased risk for CRC. The only way to establish risk in this younger population would be to design a prospective study of asymptomatic, average-risk young patients with and without DM to compare risk of adenomas and CRC. Prior published studies have also encountered this limitation. In a recent study by Gupta *et al*^[23] asymptomatic patients aged 40-49 years undergoing screening for a family history of polyps were compared to a control population of 40-49 years olds with symptoms. In addition, longitudinal studies following patients with DM over time would be needed to study more clinically significant outcomes such

as incidence of CRC and related mortality to address whether the increase in number of adenomas found in patients with DM leads to higher rates of CRC and related mortality. Such a study would require at least ten years of follow-up to answer these questions. In the meantime, retrospective cohort studies such as ours are the only means to examine a younger population of diabetics. The same may be said for studies evaluating the increased CRC risk for African Americans, in which no prospective studies have been performed. However, those retrospective studies have accumulated enough evidence to change the American College of Gastroenterology guidelines to recommend initiating CRC screening earlier at age 45 years^[4,24].

Our study controlled for age, gender, and date of procedure by design. Males have been established to have higher risk for CRC and adenomas^[11,25]. Dates of procedures were controlled to take into account different endoscopists and to decrease accrual bias. Although we adjusted our analyses by ethnicity, tobacco, alcohol, and BMI, our study did not control for additional possible confounding risk factors such as diet and exercise. There were higher rates of African-Americans in the DM cohort, but this did not reach statistical significance and ethnicity was adjusted for in the multivariate analysis. A prior study by He *et al*^[26] demonstrated increased risk of CRC associated with DM (RR 1.19), which was consistent across four ethnic populations including Caucasians, African-Americans, Japanese-Americans, and Latinos in a prospective analysis of the population-based Multiethnic Cohort. The other variables that were significantly different among our three cohorts are to be expected: age (which was a defining feature of the cohorts) as well as co-morbidities known to be associated with DM (obesity, hypertension, and hyperlipidemia). However, the ADR differences in the three cohorts still remained significant after multivariate analysis adjusted for the presence of ethnicity, BMI, smoking, and alcohol use.

In our study, we noted that the bowel preparation was poor or fair in one-third of patients with DM, causing their exclusion from the cohort. Diabetic patients may have inadequate bowel preparation due to autonomic neuropathy and gastrointestinal dysmotility associated with their DM. This may lead to decreased detection of both adenomas and CRC in patients with DM, since bowel preparation is vital to high-quality screening colonoscopy. If pre-malignant polyps are less frequently detected and removed in diabetic patients due to inadequate visibility, this may lead to the development of more interval CRC in these patients. In addition, decreased detection of both adenomas and CRC may lead to the underestimation of their risk in those with DM. At our institution, we are recommending that patients with DM undergo a more stringent bowel preparation to ensure adequate visibility and effective screening.

Our data may have important public health implications given the estimated 25.8 million people affected by DM with rapidly rising incidence in the United States^[27]. Other studies have suggested that DM increases the risk

for development of CRC and adenomatous polyps, the pre-malignant precursor to CRC. Our study confirms this increased risk in patients with DM who were up to a decade younger than the recommended screening age of 50 years. These findings need to be validated in further studies, optimally with prospective and longitudinal studies in younger diabetics that are asymptomatic and at average risk for CRC. If our results are corroborated, this high risk group may be targeted for more aggressive CRC screening.

COMMENTS

Background

Type 2 diabetes mellitus (DM), a state of hyperinsulinemia, is associated with increased risk of colorectal neoplasia including colorectal cancer (CRC) and its precursor colonic adenomas. It is unknown if patients with DM require more aggressive screening than patients at average risk for CRC.

Research frontiers

Patients with adenomas found on colonoscopy are at increased risk for developing CRC. DM is associated with increased rates of developing adenomas. The research hotspot is determining if patients with DM develop adenomas at an age earlier than the standard recommended screening age of 50 years old.

Innovations and breakthroughs

Prior studies including population and prospective cohort studies have found that DM is associated with a 20%-60% increased risk of CRC. In addition, there have been data showing a similar association with adenomatous polyps, the precursor to CRC. There is also data that this risk is elevated with greater DM severity as evidenced by insulin requirement and HgbA1C. However, none of these studies evaluated patients with or without DM under the age of 50 years.

Applications

DM was associated with increased risk for developing colorectal adenomas in patients 40-49 years old. This is the first study to specifically examine these differences among patients with or without DM younger than the recommended colorectal cancer screening age of 50 years.

Terminology

Polyp and adenoma detection rates are defined as the proportion of screened subjects in whom at least one polyp or adenoma was identified respectively. High risk state was defined as adenoma size ≥ 1 cm, number of adenomas ≥ 3 , villous features, or high grade dysplasia.

Peer review

This is a well-written manuscript on the frequency of adenoma detection in subjects with and without diabetes mellitus. The issue is relevant and data are original. The study is adequately designed with clear results.

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